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EXAMINER	
MAEWALL, SNIGDHA	

ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
06/12/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/525,021	NAKAMURA ET AL.	
	Examiner	Art Unit	
	Snigdha Maewall	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 March 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5,8,11 and 20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-2, 5, 8, 11 and 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. Receipt of Applicants arguments/Remarks and **RCE** filed on 03/16/09 are acknowledged.

Claims 3-4, 6-7, 9-10, 12-19 and 21have been canceled.

Claim 1 has been amended.

Accordingly, claims **1-2, 5, 8, 11 and 20** are being examined on the merits herein.

Claim Rejections - 35 USC § 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –
(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

3. Claims 1-2, 5, 8, 11 and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by EP 464846 by Saji et al.

Saji teaches a method of treatment of schizophrenia (see page 3, lines 1-4 and page 15). Saji et al. teaches oral preparations of the claimed compound, see page 33. The reference teaches dosage for adult daily dose to be from about 1 mg to 1000 mg, preferably from about 5 to 100 mg and in case of oral dosage to be from about 0.1 mg to 100 mg, preferably from about 0.3 mg to 50 mg, (see page 13, lines 25-30). The reference teaches in Table 4, the amount of compound 101, an antipsychotic, which is same as the instant claimed compound to be 10.3 mg/kg and similar antipsychotic compound to be 26.5 mg/kg on page 15.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 1-2, 5, 8, 11 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over EP 464846 by Saji et al.

Saji et al. teaches oral preparations of the claimed compound, see page 33. The reference teaches dosage for adult daily dose to be from about 1 mg to 1000 mg, preferably from about 5 to 100 mg and in case of oral dosage to be from about 0.1 mg to 100 mg, preferably from about 0.3 mg to 50 mg, (see page 13, lines 25-30). The reference teaches in Table 4, the amount of compound 101, an antipsychotic, which is

same as the instant claimed compound to be 10.3 mg/kg and similar antipsychotic compound to be 26.5 mg/kg on page 15.

Although the reference does not teach exactly the same range 5 mg to 120 mg, however, the reference also teaches that the dosage of the imide compound or its pharmaceutically acceptable salt varies greatly with the symptom, age and weight of the patient, the dosage form and the administration mode, see page 13, lines 25-30.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to optimize the amount of drug and arrive at the optimum dosage level by doing experimental manipulations with minimum side effects. It is to be noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 223, 235 (CCPA 1955) absent evidence to the contrary

6. Claims 1-2, 5, 8, 11 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sommerville et al. (WO 03/066039 A1) in view of Wong et al. (US 6,964,962) by itself or in view of EP 464846 by Saji et al.

It is noted that (1R,2S,3R,4S)-N-[(1R,2R)-2-[4-(1,2-benzoisothiazol-3-yl)-1-piperazinyl-methyl]-1-cyclohexylmethyl]-2,3-bicyclo[2.2.1] heptanedicarboximide hydrochloride is known in the art as SM-13496 (see page 7, lines 5-8 of the specification). Thus, SM-13496 is the hydrochloride salt of (1R,2S,3R,4S)-N-[(1R,2R)-

2-[4-(1,2-benzoisothiazol-3-yl)-1-piperazinyl-methyl]-1-cyclohexylmethyl]-2,3-bicyclo[2.2.1]heptanedicarboximide.

Sommerville et al. teach a method of treating schizophrenia comprising atypical antipsychotics, namely SM-13496 (abstract; and page 5, line 35). Sommerville et al. further teaches positive and negative symptoms are often increased during the acute phase, or the florid psychotic phase, of schizophrinia and that the method of Sommerville et al. is aimed at treatment during the acute phase of schizophrenia (page 4, lines 16-23).

Sommerville et al. do not explicitly teach the dose of SM-13496 (see page 7, lines 23-25).

Wong et al. teach 0.05 to 7500 mg/day/patient of SM-13496 can be used to treat schizophrenia (see column 4, lines 51-58; and Table in column 8, line 16), which details the daily dose of SM-13496 that can be given to the patient and thus may be a once a day administration. Moreover, Wong et al. teach 0.05 to 7500 mg/day/patient of SM-13496 can be used to schizophrenia (column 4, lines 51-58; and Table in column 8, line 16). It would have been obvious too one of ordinary skill in the art to utilize the claimed amounts of 40 and 120 mg of he claimed compound for treating schizophrenia since Wong teaches the same compound for the same disease in a broad range.

While Wong et al. teach wide range of dosage, Saji et al. disclose specific ranges of dosage to treat schizophrenia.

Saji et al. teaches oral preparations of the claimed compound, see page 33. The reference teaches in Table 4, the amount of compound 101 an antipsychotic, which is

same as the instant claimed compound to be 10.3 mg/kg and similar antipsychotic compound to be 26.5 mg/kg on page 15. The reference teaches dosage for adult daily dose to be from about 1 mg to 1000 mg, preferably from about 5 to 100 mg and in case of oral dosage to be from about 0.1 mg to 100 mg, preferably from about 0.3 mg to 50 mg, (see page 13, lines 25-30).

The reference also teaches that the dosage of the imide compound or its pharmaceutically acceptable salt varies greatly with the symptom, age and weight of the patient, the dosage form and the administration mode, see page 13, lines 25-30.

It would have been obvious to one of ordinary skill in the art to optimize the dosage range of the claimed drug in order to obtain the most efficacious dosage range by doing experimental manipulations. Based on the teachings of Wong et al. and Saji et al. one would have been motivated to perform experimental manipulations with the dosage range in order to treat schizophrenia in a most efficacious dosage amount as taught by Sommerville et al. It is to be noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 223, 235 (CCPA 1955) absent evidence to the contrary.

Response to Arguments

7. Applicant's arguments filed 03/16/09 have been fully considered but they are not persuasive.

Applicants argue that:

"Applicants submit that Saji does not remedy the deficiencies of the combination of Wong and Sommerville to establish *prima facie* obviousness because the difference between the range is not minor. Saji discloses an *extremely* broad range of compounds (almost 200 compounds), which it claims have "significant" anti-psychotic activity (See col. 12, lines 25-28; and col. 2 lines 9-15 and 64-65). In contrast to the Examiner's assertions, Saji discloses that *any one* of this broad range of compounds could be administered in "a dose of from about 1 to 1,000 mg, preferably from about 5 to 100 mg, in case of oral administration and at a daily dose of from about 0.1 to 1000 rag, preferably from about 0.3 to 50 mg, in case of intravenous injection." (Saji, col. 12, lines 19-23). Furthermore, the *in vivo* methods disclosed in Saji merely disclose "a designated amount of the test compound is orally administered." (Saji, col. 13, lines 30-31). Thus, Applicants submit that one of skill would not be able to determine which particular compound would be effective at any particular dose range from the disclosure in Saji."

Applicants arguments are not persuasive because Saji does disclose the claimed range, thus one of ordinary skill would envision based on the given dosage range of 1mg to 1000 mg of the claimed compound of prior art that any given amount that falls within the disclosed amount would work based on the teachings of the prior art.

Applicants argue that Saji does not speak to the negative symptoms of Schizophrenia. Applicant's arguments are not persuasive. Saji teaches the claimed amounts and it would have been within the purview of a skilled artisan to come to the optimum amount to treat schizophrenia. There is nothing in the Saji's reference which describes that negative symptoms were still prevailing while treating schizophrenia with the claimed compound. Patent office is not equipped with laboratory to teat the compounds. Hence the burden is on Applicant to provide the statistical analysis of the prior art and the claimed invention to present unexpected result. Since prior art discloses the same amount as claimed instantly, one of ordinary would have expected the treatment of schizophrenia with no negative side effects. Applicant argues that the declaration provided the comparison, however, it is the position of the Examiner that

the declaration and the study of maximum tolerated dose of SM-13496 is not sufficient to overcome the rejection based on the prior art since applicants have not shown comparative analysis of the prior art versus the claimed invention. Additionally, the reference by Saji et al. disclose the dosage range of the claimed compound which can be in the range of 10 mg, 20 mg and 40 mg, which overlap with the claimed dosage range of the claimed compound. The declaration fails to provide unexpected results with respect to the claimed dosage ranges to treat all the aspects of schizophrenia such as positive and negative. The declaration does not compare the Saji reference with the claimed amounts. Saji teaches the claimed amounts. Furthermore, the declaration is not supported by in vivo data to show the comparative analysis and unexpected results.

8. Claims 1-2, 5, 8, 11 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wong et al. (US 6,964,962) by itself or in view of EP 464846 by Saji et al.

Wong et al. teach 0.05 to 7500 mg/day/patient of SM-13496 can be used to treat schizophrenia (see column 4, lines 51-58; and Table in column 8, line 16), which details the daily dose of SM-13496 that can be given to the patient and thus may be a once a day administration. Moreover, Wong et al. teach 0.05 to 7500 mg/day/patient of SM-13496 can be used to schizophrenia (column 4, lines 51-58; and Table in column 8, line 16). It would have been obvious too one of ordinary skill in the art to utilize the claimed

amounts of 40 and 120 mg of he claimed compound for treating schizophrenia since Wong teaches the same compound for the same disease in a broad range.

It would have been obvious too one of ordinary skill in the art to utilize the claimed amounts of 40 and 120 mg of he claimed compound for treating schizophrenia since Wong teaches the same compound for the same disease in a broad range.

While Wong et al. teach wide range of dosage, Saji et al. disclose specific ranges of dosage to treat schizophrenia. Since Wong teaches the treatment of schizophrenia in combination and discloses a wide rage of dosage amount and teaches that the selection of the dosage of the first component is that which provides relief to the patient, the dosage of this component depends on several factors such as potency of the selected specific compound, the mode of administration, the age and weight of the patient, the severuity of the condition to be treated and this is considered to be within the skill of the artisan and one can review the existing literature on the components to determine optimal dosing (see column 6, lines 49-57) and Saji teaches the claimed drug alone in smaller dosage amounts in treating schizophrenia, one would have been motivated to optimize the amount to achieve best possible dosage amount with minimum side effects.

It would have been obvious to one of ordinary skill in the art to optimize the dosage range of the claimed drug in order to obtain the most efficacious dosage range by doing experimental manipulations. Based on the teachings of Wong et al. and Saji et al. one would have been motivated to perform experimental manipulations with the dosage range in order to treat schizophrenia in a most efficacious dosage amount. It is

to be noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 223, 235 (CCPA 1955) absent evidence to the contrary.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Snigdha Maewall whose telephone number is (571)-272-6197. The examiner can normally be reached on Monday to Friday; 8:30 a.m. to 5:00 p.m. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick Krass can be reached on (571) 272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-0580.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO

Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Snigdha Maewall/

Examiner, Art Unit 1612

/Gollamudi S Kishore/

Primary Examiner, Art Unit 1612